

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed ADACEL™



DESCRIPTION

ADACEL™, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) is a sterile liquid suspension of tetanus and diphtheria toxoids and acellular pertussis components, intended for intramuscular administration. Each antigen is adsorbed onto aluminum phosphate. After shaking, the vaccine is a white, homogenous, cloudy suspension.

Each dose of ADACEL vaccine (0.5 mL) contains the following active ingredients:

tetanus toxoid (T)	5 Lf
diphtheria toxoid (d)	2 Lf
detoxified pertussis toxin (PT)	2.5 µg
filamentous hemagglutinin (FHA)	5 µg
pertactin (PRN)	3 µg
fimbriae types 2 and 3 (FIM)	5 µg

Other ingredients per dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, ≤5 µg residual formaldehyde, <50 ng residual glutaraldehyde and 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative). The antigens are the same as those in DAPTACEL®, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP); however, ADACEL vaccine is formulated with reduced quantities of d and detoxified PT.

The 5 acellular pertussis vaccine components are obtained from *Bordetella pertussis* cultures grown in Stainer-Scholte medium (1) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture

medium. FIM are extracted from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde, FHA is treated with formaldehyde, and the residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed onto aluminum phosphate.

Corynebacterium diphtheriae is grown in modified Mueller's growth medium. (2) After purification by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde and diafiltered. *Clostridium tetani* is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (3) Tetanus toxin is detoxified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

The adsorbed diphtheria, tetanus and acellular pertussis components are combined with aluminum phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for injection.

When tested in guinea pigs, the tetanus component induces at least 2 neutralizing units/mL of serum and the diphtheria component induces at least 0.5 neutralizing units/mL of serum. The potency of the acellular pertussis vaccine components is evaluated by the antibody response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA).

CLINICAL PHARMACOLOGY

Background

In the United States, immunization against pertussis, tetanus and diphtheria became widespread in the late 1940s and resulted in a decrease in the incidence of morbidity and mortality from these diseases. Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) vaccines were first available for use in infants in the US in 1996 and have been routinely recommended for all doses of the vaccination series for infants and children <7 years of age since 1997. (4)

Tetanus

Tetanus is an acute and often fatal disease caused by an extremely potent neurotoxin produced by *C tetani*. The toxin causes neuromuscular dysfunction, with rigidity and spasms of skeletal muscles. The muscle spasms usually involve the jaw (lockjaw) and neck and then become generalized.

Spores of *C tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus toxin does not occur in the US. Thus, universal primary immunization, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect all age groups. Following immunization, protection generally persists for at least 10 years. (5)

Diphtheria

C diphtheriae may cause both localized and generalized disease. The systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C diphtheriae*. Both toxigenic and nontoxigenic strains of *C diphtheriae* can cause disease, but only strains that produce toxin can cause severe manifestations such as myocarditis and neuritis. Toxigenic strains are more often associated with severe or fatal respiratory infections than with cutaneous infections.

Complete immunization significantly reduces the risk of developing diphtheria and immunized persons who develop disease have milder illness.

Immunization with diphtheria toxoid does not, however, eliminate carriage of *C diphtheriae* in the pharynx, nose, or on the skin. Following immunization, protection lasts at least 10 years. (5)

Pertussis

Pertussis (whooping cough) is a disease of the respiratory tract, most often caused by *B pertussis*. This gram-negative coccobacillus produces a variety of biologically active components, though their role in pathogenesis is not clearly defined. Widespread use of pertussis vaccines among infants and children younger than 7 years of age led to a gradual decline in reported cases from the late 1940s through the 1970s. From 1980 through 2003, the number of pertussis cases reported annually in the US has increased, with adolescents and adults accounting for a substantial

percentage of the reported cases. (6) (7)

Mechanism of Action

Protection against disease attributable to *C tetani* is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay, is considered the minimum protective level. (8) (9) A level ≥ 0.1 to 0.2 IU/mL has been considered as protective. (10) Protection against disease attributable to *C diphtheriae* is due to the development of neutralizing antibodies to diphtheria toxin. A serum antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (9) Levels of 1.0 IU/mL have been associated with long term protection. (8) The mechanism of protection from *B pertussis* disease is not well understood. However, the pertussis components in ADACEL vaccine have been shown to prevent pertussis in infants in clinical trials with DAPTACEL vaccine. (See Clinical Studies.)

Clinical Studies

The efficacy of the tetanus toxoid and diphtheria toxoid used in ADACEL vaccine was based on the immune response to these antigens compared to a US licensed Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) vaccine manufactured by Aventis Pasteur Inc., Swiftwater, PA. The primary measures of immunogenicity were (a) the percentage of subjects attaining an antibody level of at least 0.1 IU/mL and (b) the percentage of subjects achieving a rise in antibody concentration after vaccination (booster response). The demonstration of a booster response depended on the antibody concentration to each antigen prior to immunization. Threshold or “cut-off” values for antibody concentrations to each antigen were established based on the 95th percentile of the pre-vaccination antibody concentrations observed in previous clinical trials. A booster response was defined as a four-fold rise in antibody concentration if the pre-vaccination concentration was below the cut-off value and a two-fold rise in antibody concentration if the pre-vaccination concentration was above the cut-off value.

The efficacy of the pertussis antigens used in ADACEL vaccine was inferred based on a comparison of pertussis antibody levels achieved in recipients of a single booster dose of ADACEL vaccine with those obtained in infants after three doses of DAPTACEL vaccine. In the

Sweden I Efficacy Trial, three doses of DAPTACEL vaccine was shown to confer a protective efficacy of 84.9% (95% CI: 80.1%, 88.6%) against WHO defined pertussis (21 days of paroxysmal cough with laboratory-confirmed *B pertussis* infection or epidemiological link to a confirmed case). The protective efficacy against mild pertussis (defined as at least one day of cough with laboratory-confirmed *B pertussis* infection) was 77.9% (95% CI: 72.6%, 82.2%). (11) (12) In addition, the ability of ADACEL vaccine to elicit a booster response to the pertussis antigens following vaccination was evaluated. The acellular pertussis formulations for ADACEL and DAPTACEL vaccines differ only in the amount of detoxified PT (2.5 µg in ADACEL vaccine versus 10 µg in DAPTACEL vaccine).

The principal immunogenicity study was a comparative, multi-center, randomized, observer blind, controlled trial that enrolled male and female adolescents and adults, 11-64 years of age inclusive, who had not received tetanus or diphtheria toxoid-containing vaccines within 5 years.

Participants were vaccinated with either a dose of ADACEL vaccine (N = 1,268) or Td vaccine (N = 1,023). (Blinding procedures for safety assessments are described in the ADVERSE REACTIONS section.) Participants were randomized between groups. The study also included age stratification to ensure adequate representation across the entire age range of 11-64. Sera were obtained before and approximately 35 days after vaccination.

For subjects enrolled in this comparative trial, demographic characteristics were similar between the vaccine groups. The immunogenicity profiles for tetanus and diphtheria toxoids between ADACEL and Td vaccines were comparable. (See Table 1 and Table 2.) ADACEL vaccine induced pertussis antibodies that exceeded those after three doses of DAPTACEL vaccine. (See Table 3.) Acceptable booster responses to each of the pertussis antigens were also demonstrated, ie, the percentage of subjects with a booster response exceeded the pre-defined lower limit. (12) (See Table 4.)

Table 1: Tetanus Antitoxin Levels and Booster Response Rates

			Tetanus Antitoxin (IU/mL)				
			Pre-Vaccination		1 Month Post-Vaccination		
Age Group (years)	Vaccine	N	% ≥ 0.10 (95% CI)	% ≥ 1.0 (95% CI)	% ≥ 0.10 (95% CI)	% ≥ 1.0 (95% CI)	% Booster* (95% CI)
11-17	ADACEL	527	99.6 (98.6, 100.0)	44.6 (40.3, 49.0)	100.0† (99.3, 100.0)	99.6‡ (98.6, 100.0)	91.7 (89.0, 93.9)
	Td	516	99.2 (98.0, 99.8)	43.8 (39.5, 48.2)	100.0 (99.3, 100.0)	99.4 (98.3, 99.9)	91.3 (88.5, 93.6)
18-64	ADACEL	742	97.3 (95.9, 98.3)	72.9 (69.6, 76.1)	100.0† (99.5, 100.0)	97.8‡ (96.5, 98.8)	63.1 (59.5, 66.6)
	Td	509	95.9 (93.8, 97.4)	70.3 (66.2, 74.3)	99.8 (98.9, 100.0)	98.2 (96.7, 99.2)	66.8 (62.5, 70.9)

* Booster response is defined as: A four-fold rise in antibody concentration, if the pre-vaccination concentration was below the cut-off value, and a two-fold rise in antibody concentration if the pre-vaccination concentration was above the cut-off value. The cut-off value for tetanus was 2.7 IU/mL.

† Seroprotection rates at ≥ 0.10 IU/mL or booster response rates to ADACEL vaccine were non-inferior to Td vaccine (upper limit of the 95% CI on the difference for Td vaccine minus ADACEL vaccine $<10\%$).

‡ Seroprotection rates at ≥ 1.0 IU/mL were not designed as a primary endpoint; however, ADACEL vaccine met non-inferiority criteria (upper limit of the 95% CI on the difference for Td vaccine minus ADACEL vaccine $<10\%$) at this level.

Table 2: Diphtheria Antitoxin Levels and Booster Response Rates

			Diphtheria Antitoxin (IU/mL)				
			Pre-Vaccination		1 Month Post-Vaccination		
Age Group (years)	Vaccine	N	% ≥ 0.10 (95% CI)	% ≥ 1.0 (95% CI)	% ≥ 0.10 (95% CI)	% ≥ 1.0 (95% CI)	% Booster* (95% CI)
11-17	ADACEL	527	72.5 (68.5, 76.3)	15.7 (12.7, 19.1)	99.8† (98.9, 100.0)	98.7‡ (97.3, 99.5)	95.1 (92.9, 96.8)
	Td	516	70.7 (66.5, 74.6)	17.3 (14.1, 20.8)	99.8 (98.9, 100.0)	98.4 (97.0, 99.3)	95.0 (92.7, 96.7)
18-64	ADACEL	741	62.6 (59.0, 66.1)	14.3 (11.9, 17.0)	94.1† (92.1, 95.7)	78.0‡ (74.8, 80.9)	87.4 (84.8, 89.7)
	Td	507	63.3 (59.0, 67.5)	16.0 (12.9, 19.5)	95.1 (92.8, 96.8)	79.9 (76.1, 83.3)	83.4 (79.9, 86.5)

* Booster response is defined as: A four-fold rise in antibody concentration, if the pre-vaccination concentration was below the cut-off value, and a two-fold rise in antibody concentration if the pre-vaccination concentration was above the cut-off value. The cut-off value for diphtheria was 2.56 IU/mL.

† Seroprotection rates at ≥ 0.10 IU/mL and booster response rates to ADACEL vaccine were non-inferior to Td vaccine (upper limit of the 95% CI on the difference for Td vaccine minus ADACEL vaccine $< 10\%$).

‡ Seroprotection rates at ≥ 1.0 IU/mL were not designed as a primary endpoint, however ADACEL vaccine met non-inferiority criteria (upper limit of the 95% CI on the difference for Td vaccine minus ADACEL vaccine $< 10\%$) at this level.

Table 3: Ratio of Pertussis Antibody Geometric Mean Concentrations (GMCs)‡ Observed One Month After a Dose of ADACEL Vaccine in Adolescents and Adults Compared with Those Observed in Infants One Month Following Three Doses at 2, 4 and 6 Months of Age in an Efficacy Trial with DAPTACEL Vaccine

	Adolescents ADACEL/DAPTACEL GMC Ratio* (95% CIs)	Adults ADACEL/DAPTACEL GMC Ratio* (95% CIs)
Anti-PT	3.6 (2.8, 4.5)†	2.1 (1.6, 2.7)†
Anti-FHA	5.4 (4.5, 6.5)†	4.8 (3.9, 5.9)†
Anti-PRN	3.2 (2.5, 4.1)†	3.2 (2.3, 4.4)†
Anti-FIM	5.3 (3.9, 7.1)†	2.5 (1.8, 3.5)†

* The ratios of GMC were determined for adolescents compared to infants, as well as for adults compared to infants.

† GMC following ADACEL vaccine was non-inferior to GMC following DAPTACEL vaccine (lower limit of 95% CI on the ratio of GMC for ADACEL vaccine divided by DAPTACEL vaccine >0.67).

‡ Antibody GMCs, measured in arbitrary ELISA units were calculated separately for infants, adolescents and adults.

Table 4: Booster Responses to the Pertussis Antigens Observed One Month After a Dose of ADACEL Vaccine in Adolescents and Adults

	Adolescents N = 524 % (95% CI)	Adults N = 739 % (95% CI)	Pre-defined Acceptable Rates* %†
Anti-PT	92.0 (89.3, 94.2)	84.4 (81.6, 87.0)	81.2
Anti-FHA	85.6 (82.3, 88.4)	82.7 (79.8, 85.3)	77.6
Anti-PRN	94.5 (92.2, 96.3)	93.8 (91.8, 95.4)	86.4
Anti-FIM	94.9 (92.6, 96.6)	85.9 (83.2, 88.4)	82.4

* The acceptable response rate for each antigen was defined as the lower limit of the 95% CI for the rate being no more than 10% lower than the response rate observed in previous clinical trials.

† A booster response for each antigen was defined as a four-fold rise in antibody concentration if the pre-vaccination concentration was below the cut-off value and a two-fold rise in antibody concentration if the pre-vaccination concentration was above the cut-off value. The cut-off values for pertussis antigens were established based on antibody data from both adolescents and adults in previous clinical trials. The cut-off values were 85 EU/mL for PT, 170 EU/mL for FHA, 115 EU/mL for PRN and 258 EU/mL for FIM

CONCURRENTLY ADMINISTERED VACCINES

Hepatitis B Vaccine

The concomitant use of ADACEL vaccine and hepatitis B (Hep B) vaccine (Recombivax HB[®], 10 µg per dose using a two-dose regimen, manufactured by Merck and Co., Inc) was evaluated in a multi-center, open-labeled, randomized, controlled study that enrolled 410 adolescents, 11-14 years of age inclusive. One group received ADACEL and Hep B vaccines concurrently (N = 206). The other group (N = 204) received ADACEL vaccine at the first visit, then 4-6 weeks later received Hep B vaccine. The second dose of Hep B vaccine was given 4-6 weeks after the first dose. Serum samples were obtained prior to and 4-6 weeks after ADACEL vaccine administration, as well as 4-6 weeks after the 2nd dose of Hep B for all subjects. No interference was observed in the immune responses to any of the vaccine antigens when ADACEL and Hep B vaccines were given concurrently or separately. (12) (See DOSAGE AND ADMINISTRATION, Concomitant Vaccine Administration.)

Trivalent Inactivated Influenza Vaccine

The concomitant use of ADACEL vaccine and trivalent inactivated influenza vaccine (TIV, Fluzone[®], manufactured by Aventis Pasteur Inc., Swiftwater, PA) was evaluated in a multi-center, open-labeled, randomized, controlled study conducted in 720 adults, 19-64 years of age inclusive. In one group, subjects received ADACEL and TIV vaccines concurrently (N = 359). The other group received TIV at the first visit, then 4-6 weeks later received ADACEL vaccine (N = 361). Sera were obtained prior to and 4-6 weeks after ADACEL vaccine, as well as 4-6 weeks after the TIV. The immune responses were comparable for concurrent and separate administration of ADACEL and TIV vaccines for diphtheria (percent of subjects with seroprotective concentration ≥ 0.1 IU/mL and booster responses), tetanus (percent of subjects with seroprotective concentration ≥ 0.1 IU/mL), pertussis antigens (booster responses and GMCs except lower PRN GMC in the concomitant group, lower bound of the 90% CI was 0.61 and the pre-specified criterion was ≥ 0.67) and influenza antigens (seroprotection and seroconversion rates). Although tetanus booster response rates were significantly lower in the group receiving the vaccines concurrently versus separately, greater than 98% of subjects in both groups achieved seroprotective levels of

≥0.1 IU/mL. (12) (See DOSAGE AND ADMINISTRATION, Concomitant Vaccine Administration.)

INDICATIONS AND USAGE

ADACEL vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria and pertussis as a single dose in persons 11 through 64 years of age.

The use of ADACEL vaccine as a primary series, or to complete the primary series, has not been studied.

See DOSAGE AND ADMINISTRATION for use in tetanus prophylaxis in wound management.

ADACEL vaccine is not indicated for the treatment of *B pertussis*, *C diphtheriae* or *C tetani* infections.

As with any vaccine, ADACEL vaccine may not protect 100% of vaccinated individuals.

CONTRAINDICATIONS

Known systemic hypersensitivity to any component of ADACEL vaccine or a life-threatening reaction after previous administration of the vaccine or a vaccine containing the same substances are contraindications to vaccination with ADACEL vaccine. Because of uncertainty as to which component of the vaccine may be responsible, additional vaccinations with the diphtheria, tetanus or pertussis components should not be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.

The following events are contraindications to administration of any pertussis containing vaccine:

(10)

- Encephalopathy not attributable to another identifiable cause within 7 days of administration of a previous dose.
- Progressive neurological disorder, uncontrolled epilepsy, or progressive encephalopathy. Pertussis vaccine should not be administered to individuals with these conditions until a

treatment regimen has been established, the condition has stabilized, and the benefit clearly outweighs the risk.

ADACEL vaccine is not contraindicated for use in individuals with HIV infection. (10)

WARNINGS

Because intramuscular injection can cause injection site hematoma, ADACEL vaccine should not be given to persons with any bleeding disorder, such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefits clearly outweigh the risk of administration. If the decision is made to administer ADACEL vaccine in such persons, it should be given with caution, with steps taken to avoid the risk of hematoma formation following injection. (10)

If any of the following events occurred in temporal relation to previous receipt of a vaccine containing a whole-cell pertussis (eg. DTP) or an acellular pertussis component, the decision to give ADACEL vaccine should be based on careful consideration of the potential benefits and possible risks: (4) (13)

- Temperature of $\geq 40.5^{\circ}\text{C}$ (105°F) within 48 hours not due to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours;
- Seizures with or without fever occurring within 3 days.

When a decision is made to withhold pertussis vaccine, Td vaccine should be given.

Persons who experienced Arthus-type hypersensitivity reactions (eg., severe local reactions associated with systemic symptoms) (14) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given emergency doses of tetanus toxoid-containing vaccines more frequently than every 10 years, even if the wound is neither clean nor minor. (5) (14)

If Guillain-Barré Syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give subsequent doses of ADACEL vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible

risks. (10)

The decision to administer a pertussis-containing vaccine to individuals with stable central nervous system (CNS) disorders must be made by the health-care provider on an individual basis, with consideration of all relevant factors and assessment of potential risks and benefits for that individual. The ACIP has issued guidelines for immunizing such individuals. (4)

A family history of seizures or other CNS disorders is not a contraindication to pertussis vaccine. (4)

The ACIP has published guidelines for vaccination of persons with recent or acute illness. (10)

PRECAUTIONS

General

Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

ADACEL vaccine should not be administered into the buttocks nor by the intradermal route, since these methods of administration have not been studied; a weaker immune response has been observed when these routes of administration have been used with other vaccines. (10)

The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents and equipment should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

Prior to administration of any dose of ADACEL vaccine, the vaccine recipient and/or the parent or guardian must be asked about personal health history, including immunization history, current health status and any adverse event after previous immunizations. In persons who have a history of serious or severe reaction within 48 hours of a previous injection with a vaccine containing similar components, administration of ADACEL vaccine must be carefully considered.

The ACIP has published guidelines for the immunization of immunocompromised individuals.(15) Immune responses to inactivated vaccines and toxoids when given to immunocompromised persons may be suboptimal. (10) The immune response to ADACEL vaccine administered to

immunocompromised persons (whether from disease or treatment) has not been studied.

A separate, sterile syringe and needle, or a sterile disposable unit, must be used for each person to prevent transmission of blood borne infectious agents. Needles should not be recapped but should be disposed of according to biohazard waste guidelines.

Information for Vaccine Recipients and/or Parent or Guardian

Before administration of ADACEL vaccine, health-care providers should inform the vaccine recipient and/or parent or guardian of the benefits and risks.

The health-care provider should inform the vaccine recipient and/or parent or guardian about the potential for adverse reactions that have been temporally associated with ADACEL vaccine or other vaccines containing similar components. The vaccine recipient and/or parent or guardian should be instructed to report any serious adverse reactions to their health-care provider. Females of childbearing potential should be informed that Aventis Pasteur Inc. maintains a pregnancy registry to monitor fetal outcomes of pregnant women exposed to ADACEL vaccine. If they are pregnant or become aware they were pregnant at the time of ADACEL vaccine immunization, they should contact their health-care professional or Aventis Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE).

The health-care provider should provide the Vaccine Information Statements (VISs) that are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization.

The US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. (16) The toll-free number for VAERS forms and information is 1-800-822-7967 or visit the VAERS website at <http://www.fda.gov/cber/vaers/vaers.htm>

Drug Interactions

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. (See PRECAUTIONS, General.)

For information regarding simultaneous administration with other vaccines refer to the CLINICAL PHARMACOLOGY– Concurrently Administered Vaccines, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed with ADACEL vaccine to evaluate carcinogenicity, mutagenic potential, or impairment of fertility.

Pregnancy Category C

Animal reproduction studies have not been conducted with ADACEL vaccine. It is also not known whether ADACEL vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ADACEL vaccine should be given to a pregnant woman only if clearly needed. Animal fertility studies have not been conducted with ADACEL vaccine. The effect of ADACEL vaccine on embryo-fetal and pre-weaning development was evaluated in two developmental toxicity studies using pregnant rabbits. Animals were administered ADACEL vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29, 0.5 mL/rabbit/occasion (a 17-fold increase compared to the human dose of ADACEL vaccine on a body weight basis), by intramuscular injection. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study. (12)

Pregnancy Registry

Health-care providers are encouraged to register pregnant women who receive ADACEL vaccine in Aventis Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463 (1-800-VACCINE).

Nursing Mothers

It is not known whether ADACEL vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ADACEL vaccine is given to a nursing woman.

Pediatric Use

ADACEL vaccine is not indicated for individuals less than 11 years of age. (See INDICATIONS AND USAGE.) For immunization of persons 6 weeks through 6 years of age against diphtheria, tetanus and pertussis, a Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) may be used, unless otherwise contraindicated.

Geriatric Use

ADACEL vaccine is not indicated for individuals 65 years of age and older. No data are available regarding the safety and effectiveness of ADACEL vaccine in individuals 65 years of age and older as clinical studies of ADACEL vaccine did not include subjects in the geriatric population.

ADVERSE REACTIONS

The safety of ADACEL vaccine was evaluated in 4 clinical studies. A total of 5,841 individuals 11-64 years of age inclusive (3,393 adolescents 11-17 years of age and 2,448 adults 18-64 years) received a single booster dose of ADACEL vaccine.

The principal safety study was a randomized, observer blind, active controlled trial that enrolled participants 11-17 years of age (ADACEL vaccine N = 1,184; Td vaccine N = 792) and 18-64 years of age (ADACEL vaccine N = 1,752; Td vaccine N = 573). Study participants had not received tetanus or diphtheria containing vaccines within the previous 5 years. Observer blind design, ie, study personnel collecting the safety data differed from personnel administering the vaccines, was used due to different vaccine packaging (ADACEL vaccine supplied in single dose vials; Td vaccine supplied in multi-dose vials). Solicited local and systemic reactions were monitored daily for 14 days post-vaccination using a diary card. Participants were monitored for 28 days for adverse events which were not specifically queried on the diary card, ie, unsolicited adverse events, and for 6 months post-vaccination for visits to an emergency room, unexpected

visits to an office physician, hospitalization and serious adverse events. Unsolicited adverse event information was obtained either by telephone interview or at an interim clinic visit. Information regarding adverse events that occurred in the 6 month post-vaccination time period was obtained via a scripted telephone interview. Approximately 96% of participants completed the 6-month follow-up evaluation.

In the concomitant vaccination study with ADACEL and Hepatitis B vaccines (see Clinical Studies for description of study design and number of participants), local and systemic adverse events were monitored daily for 14 days post vaccination using a diary card. Local adverse events were only monitored at site/arm of ADACEL vaccine administration. Unsolicited reactions (including immediate reactions, serious adverse events and events that elicited seeking medical attention) were collected at a clinic visit or via telephone interview for the duration of the trial, ie up to six months post-vaccination.

In the concomitant vaccination study with ADACEL vaccine and trivalent inactivated influenza vaccines (see Clinical Studies for description of study design and number of participants), local and systemic adverse events were monitored for 14 days post vaccination using a diary card. All unsolicited reactions occurring through day 14 were collected. From day 14 to the end of the trial, ie, up to 84 days, only events that elicited seeking medical attention were collected.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

Serious Adverse Events in All Safety Studies

Throughout the 6-month follow-up period in the principal safety study, serious adverse events were reported in 1.5% of ADACEL vaccine recipients and 1.4% in Td vaccine recipients. Two serious adverse events in adults were neuropathic events that occurred within 28 days of ADACEL vaccine administration; one severe migraine with unilateral facial paralysis and one diagnosis of nerve compression in neck and left arm. Similar or lower rates of serious adverse events were reported in the other trials and there were no additional neuropathic events reported.

Solicited Adverse Events in the Principal Safety Study

The frequency of selected solicited adverse events (erythema, swelling, pain and fever) occurring during Days 0-14 following one dose of ADACEL vaccine or Td vaccine are presented in Table 5. Most of these events were reported at a similar frequency in recipients of both ADACEL vaccine and Td vaccine. Few participants (<1%) sought medical attention for these reactions. Pain at the injection site was the most common adverse reaction occurring in 62-78% of all vaccinees. In addition, overall rates of pain were higher in adolescent recipients of ADACEL vaccine compared to Td vaccine recipients. Rates of moderate and severe pain in adolescents did not significantly differ between the two groups. Rates of pain did not significantly differ for adults. Fever of 38°C and higher was uncommon, although in the adolescent age group, it occurred significantly more frequently in ADACEL vaccine recipients than Td vaccine recipients.(12)

Table 5: Frequencies of Solicited Injection Site Reactions and Fever for Adolescents and Adults, Days 0-14, Following a Single Dose of ADACEL Vaccine or Td Vaccine

Adverse Event*		Adolescents 11-17 years		Adults 18-64 years	
		ADACEL N = 1,184 (%)	Td N = 792 (%)	ADACEL N = 1,752 (%)	Td N = 573 (%)
Injection Site Pain	Any	77.8†	71.0	65.7	62.9
	Moderate‡	18.0	15.6	15.1	10.2
	Severe§	1.5	0.6	1.1	0.9
Injection Site Swelling	Any	20.9	18.3	21.0	17.3
	Moderate‡				
	1.0 to 3.4 cm	6.5	5.7	7.6	5.4
	Severe§				
	≥3.5 cm	6.4	5.5	5.8	5.5
	≥5 cm (2 inches)	2.8	3.6	3.2	2.7
Injection Site Erythema	Any	20.8	19.7	24.7	21.6
	Moderate‡				
	1.0 to 3.4 cm	5.9	4.6	8.0	8.4
	Severe§				
	≥3.5 cm	6.0	5.3	6.2	4.8
	≥5 cm (2 inches)	2.7	2.9	4.0	3.0
Fever	≥38.0°C (≥100.4°F)	5.0†	2.7	1.4	1.1
	≥38.8°C to ≤39.4°C (≥102.0°F to ≤103.0°F)	0.9	0.6	0.4	0.2
	≥39.5°C (≥103.1°F)	0.2	0.1	0.0	0.2

* Sample size was designed to detect >10% differences between ADACEL and Td vaccines for events of ‘Any’ intensity.

† ADACEL vaccine did not meet the non-inferiority criterion for rates of ‘Any Pain’ in Adolescents compared to Td Vaccine rates (upper limit of the 95% CI on the difference for ADACEL vaccine minus Td vaccine was 10.7% whereas the criterion was <10%). For ‘Any’ fever the non-inferiority criteria was met, however, ‘Any’ fever was statistically higher in adolescents receiving ADACEL vaccine.

‡ Interfered with activities, but did not necessitate medical care or absenteeism.

§ Incapacitating, prevented the performance of usual activities, may have/or did necessitate medical care or absenteeism.

The frequency of other solicited adverse events (Days 0-14) are presented in Table 6. The rates of these events following ADACEL vaccine were comparable with those observed with Td vaccine. Headache was the most frequent systemic reaction and was usually of mild to moderate intensity.

Table 6: Frequencies of Other Solicited Adverse Events for Adolescents and Adults, Days 0-14, Following a Single Dose of ADACEL Vaccine or Td Vaccine

Adverse Event		Adolescents 11-17 years		Adults 18-64 years	
		ADACEL N = 1,184 (%)	Td N = 792 (%)	ADACEL N = 1,752 (%)	Td N = 573 (%)
Headache	Any	43.7	40.4	33.9	34.1
	Moderate*	14.2	11.1	11.4	10.5
	Severe†	2.0	1.5	2.8	2.1
Body Ache or Muscle Weakness	Any	30.4	29.9	21.9	18.8
	Moderate*	8.5	6.9	6.1	5.7
	Severe†	1.3	0.9	1.2	0.9
Tiredness	Any	30.2	27.3	24.3	20.7
	Moderate*	9.8	7.5	6.9	6.1
	Severe†	1.2	1.0	1.3	0.5
Chills	Any	15.1	12.6	8.1	6.6
	Moderate*	3.2	2.5	1.3	1.6
	Severe†	0.5	0.1	0.7	0.5
Sore and Swollen Joints	Any	11.3	11.7	9.1	7.0
	Moderate*	2.6	2.5	2.5	2.1
	Severe†	0.3	0.1	0.5	0.5
Nausea	Any	13.3	12.3	9.2	7.9
	Moderate*	3.2	3.2	2.5	1.8
	Severe†	1.0	0.6	0.8	0.5
Lymph Node Swelling	Any	6.6	5.3	6.5	4.1
	Moderate*	1.0	0.5	1.2	0.5

		Adolescents 11-17 years		Adults 18-64 years	
		Severe†			
Diarrhea	Any	10.3	10.2	10.3	11.3
	Moderate*	1.9	2.0	2.2	2.7
	Severe†	0.3	0.0	0.5	0.5
Vomiting	Any	4.6	2.8	3.0	1.8
	Moderate*	1.2	1.1	1.0	0.9
	Severe†	0.5	0.3	0.5	0.2
Rash	Any	2.7	2.0	2.0	2.3

* Interfered with activities, but did not necessitate medical care or absenteeism.

† Incapacitating, prevented the performance of usual activities, may have/or did necessitate medical care or absenteeism.

Local and systemic solicited reactions occurred at similar rates in ADACEL vaccine and Td vaccine recipients in the 3 day post-vaccination period. Most local reactions occurred within the first 3 days after vaccination (with a mean duration of less than 3 days).

Adverse Events in the Concomitant Vaccine Studies

Local and Systemic Reactions when Given with Hepatitis B Vaccine

The rates reported for fever and injection site pain (at the ADACEL vaccine administration site) were similar when ADACEL and Hep B vaccines were given concurrently or separately. However, the rates of injection site erythema (23.4% for concomitant vaccination and 21.4% for separate administration) and swelling (23.9% for concomitant vaccination and 17.9% for separate administration) at the ADACEL vaccine administration site were increased when co-administered. Swollen and/or sore joints were reported by 22.5% for concomitant vaccination and 17.9% for separate administration. The rates of generalized body aches in the individuals who reported swollen and/or sore joints were 86.7% for concomitant vaccination and 72.2% for separate administration. Most joint complaints were mild in intensity with a mean duration of 1.8 days. The incidence of other solicited and unsolicited adverse events were not different between the 2 study groups. (12)

Local and Systemic Reactions when Given with Trivalent Inactivated Influenza Vaccine

The rates of fever and injection site erythema and swelling were similar for recipients of concurrent and separate administration of ADACEL vaccine and TIV. However, pain at the ADACEL vaccine injection site occurred at statistically higher rates following concurrent administration (66.6%) versus separate administration (60.8%). The rates of sore and/or swollen joints were 13% for concurrent administration and 9% for separate administration. Most joint complaints were mild in intensity with a mean duration of 2.0 days. The incidence of other solicited and unsolicited adverse events were similar between the 2 study groups. (12)

Additional Studies

An additional 1,806 adolescents received ADACEL vaccine as part of the lot consistency study used to support ADACEL vaccine licensure. This study was a randomized, double-blind, multi-

center trial designed to assess lot consistency as measured by the safety and immunogenicity of 3 lots of ADACEL vaccine when given as a booster dose to adolescents 11-17 years of age inclusive. Local and systemic adverse events were monitored for 14 days post vaccination using a diary card. Unsolicited adverse events and serious adverse events were collected for 28 days post vaccination. Pain was the most frequently reported local adverse event occurring in approximately 80% of all subjects. Headache was the most frequently reported systemic event occurring in approximately 44% of all subjects. Sore and/or swollen joints were reported by approximately 14% of participants. Most joint complaints were mild in intensity with a mean duration of 2.0 days. (12)

An additional 962 adolescents and adults received ADACEL vaccine in three supportive Canadian studies used as the basis for licensure in other countries. Within these clinical trials, the rates of local and systemic reactions following ADACEL vaccine were similar to those reported in the four principal trials in the US with the exception of a higher rate (86%) of adults experiencing 'any' local injection site pain. The rate of severe pain (0.8%), however, was comparable to the rates reported in the four principal trials. (12)

Postmarketing Reports

In addition to the data from clinical trials, the following adverse events have spontaneously been reported during the commercial use of ADACEL vaccine in other countries. These adverse events have been very rarely reported (<0.01%), however, incidence rates cannot precisely be calculated. The reported rate is based on the number of adverse event reports per estimated number of vaccinated patients.

General disorders and administration site conditions:

- injection site bruising, sterile abscess

Skin and subcutaneous tissue disorders:

- pruritus, urticaria

Additional Adverse Events

Additional adverse reactions, included in this section, have been reported in conjunction with receipt of vaccines containing diphtheria, tetanus toxoids and/or pertussis antigens.

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid. Such reactions may be associated with high levels of circulating antitoxin in persons who have had overly frequent injections of tetanus toxoid. (17) (See WARNINGS.)

Persistent nodules at the site of injection have been reported following the use of adsorbed products. (5)

Cases of allergic or anaphylactic reaction (ie, hives, swelling of the mouth, difficulty breathing, hypotension, or shock) have been reported after receiving some preparations containing diphtheria tetanus toxoids and/or pertussis antigens. (5) Death following vaccine-caused anaphylaxis has been reported. (17)

Certain neurological conditions have been reported in temporal association with some tetanus toxoid-containing vaccines or tetanus and diphtheria toxoid-containing vaccines. A review by the Institute of Medicine (IOM) concluded that the evidence favors acceptance of a causal relation between tetanus toxoid and both brachial neuritis and Guillian-Barré syndrome. Other neurological conditions that have been reported include: demyelinating diseases of the central nervous system, peripheral mononeuropathies, cranial mononeuropathies and EEG disturbances with encephalopathy (with or without permanent intellectual and/or motor function impairment). The IOM has concluded that the evidence is inadequate to accept or reject a causal relation between these conditions and vaccines containing tetanus and/or diphtheria toxoids. In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology. (17)

Reporting of Adverse Events

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records of the manufacturer and lot number of the vaccine administered in the vaccine recipient's permanent medical record along with the date of administration of the vaccine and the name, address and title of the person administering the vaccine. The Act further requires the health-care professional to report to the US Department of Health and Human Services the occurrence following immunization of any event set forth in the

Vaccine Injury Table. These include anaphylaxis or anaphylactic shock within 7 days; brachial neuritis within 28 days; an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this ADACEL vaccine package insert. (16) (18) (19)

The US Department of Health and Human Services has established the Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. Reporting of all adverse events occurring after vaccine administration is encouraged from vaccine recipients, parents/guardians and the health-care provider. Adverse events following immunization should be reported to VAERS. Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967 or visit the VAERS website at <http://www.fda.gov/cber/vaers/vaers.htm>. (16) (18) (19)

Health-care providers should also report these events to Pharmacovigilance Department, Aventis Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463 (1-800-VACCINE).

DOSAGE AND ADMINISTRATION

ADACEL vaccine should be administered as a single injection of one dose (0.5 mL) by the intramuscular route.

SHAKE THE VIAL WELL to distribute the suspension uniformly before withdrawing the 0.5 mL dose for administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. (See DESCRIPTION.) If these conditions exist, the vaccine should not be administered.

When administering a dose from a stoppered vial, do not remove either the stopper or the metal seal holding it in place.

The needle length should be sufficient to deliver the vaccine intramuscularly, but not so long as to involve underlying nerves and blood vessels or bone. The health-care professional should determine the appropriate size and length of the needle for each individual.

Aseptic technique must be used for withdrawal of each dose.

The preferred site is into the deltoid muscle. The vaccine should not be injected into the gluteal area or areas where there is a major nerve trunk.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide.

Do NOT administer this product intravenously or subcutaneously.

Needles should not be recapped and should be disposed of properly.

Five years should have elapsed since the recipient's last dose of tetanus toxoid, diphtheria toxoid and/or pertussis containing vaccine.

There are no data to support repeat administration of ADACEL vaccine.

The use of ADACEL vaccine as a primary series or to complete the primary series for tetanus, diphtheria, or pertussis has not been studied.

For individuals planning to travel to developing countries, a one-time booster dose of ADACEL vaccine may be considered if more than 5 years has lapsed since receipt of the previous dose of diphtheria toxoids, tetanus toxoids or pertussis-containing vaccine.

Diphtheria Prophylaxis for Case Contacts

The ACIP has published recommendations on vaccination for diphtheria prophylaxis in individuals who have had contact with a person with confirmed or suspected diphtheria. (5)

Tetanus Prophylaxis in Wound Management

Clinicians should refer to guidelines for tetanus prophylaxis in routine wound management. (5)(14)

A thorough attempt must be made to determine whether a patient has completed primary immunization. Individuals who have completed primary immunization against tetanus and who sustain wounds that are minor and uncontaminated, should receive a booster dose of a tetanus toxoid-containing preparation if they have not received tetanus toxoid within the preceding 10 years. For tetanus prone wounds (eg., wounds contaminated with dirt, feces, soil and saliva, puncture wounds, avulsions and wounds resulting from missiles, crushing, burns or frostbite), a booster is appropriate if the patient has not received a tetanus toxoid-containing preparation within the preceding 5 years. (5)

ADACEL vaccine can be used as a one-time alternative to Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td) vaccine in patients for whom the pertussis component is also indicated. (See INDICATIONS AND USAGE.)

If passive protection against tetanus is required, Tetanus Immune Globulin (Human) (TIG) may be administered at a separate site with a separate needle and syringe.

CONCOMITANT VACCINE ADMINISTRATION

Safety and immunogenicity data are available on concomitant administration of ADACEL vaccine with Hepatitis B (10 µg, two dose regimen) and trivalent inactivated influenza vaccines (TIV). (See CLINICAL PHARMACOLOGY and ADVERSE REACTIONS sections.)

Concurrent immunization of ADACEL vaccine with Hepatitis B vaccine did not result in reduced antibody responses to any of the antigens from either vaccine. (12)

No interference in tetanus, diphtheria and influenza vaccine seroprotection rates and responses to detoxified PT, FIM or FHA were observed when ADACEL vaccine was administered concurrently with TIV compared to separate administration. A lower PRN GMC was observed when ADACEL vaccine was administered concurrently with TIV compared to separate administration. (12)

The safety and effectiveness of co-administration of ADACEL vaccine with other vaccines have not been evaluated.

Separate injection sites and separate syringes must be used in case of concurrent administration.

STORAGE

Store between 2° - 8°C (35° - 46°F). DO NOT FREEZE. Discard product if exposed to freezing.

Do not use after expiration date.

HOW SUPPLIED

The stopper of the vial for this product does not contain natural latex rubber.

Vial, 5 x 1 Dose – Product No. 49281-400-05

Vial, 10 x 1 Dose – Product No. 42981-400-10

CPT[®] Code: 90715

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